Grape Pomace Polyphenols Benefic Actions

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Contributor: Veronica Sanda Chedea, Ștefan Octavian Macovei, Ioana Corina Bocșan, Dan Claudiu Măgureanu, Antonia Mihaela Levai, Anca Dana Buzoianu, Raluca Maria Pop

Grape pomace polyphenols research studies have grown in the last decades, given their potential benefic effects on promoting human health. Some of their benefic actions are observed in oxidative stress and inflammation aiming at homeostasis restoration. Regarding the antioxidant effect, polyphenols can modulate the endogenous pathway responsible for combating oxidative stress. These effects can be achieved by polyphenols capacity to activate the nuclear factor E2 and to up-regulate superoxide dismutase, catalase, glutathione, glutathione peroxidase, and heme-oxidase 1 or their capacity to scavenge and chelate reactive oxygen species involved in ROS production. In inflammation, polyphenols are reported to inhibit the mitogen-activated kinase pathway, Nf-kB, anddown-regulate cytokines and chemokines. Polyphenols also inhibit cyclooxygenase and lipoxygenase, which are involved in the arachidonic acid signaling pathway, being responsible for synthesizing prostaglandin, thromboxane A2, and leukotrienes which further increase inflammatory response.

Keywords: grape pomace ; polyphenols ; antioxidant ; anti-inflammatory

1. In Vitro Beneficial Actions of Grape Pomace in Oxidative Stress and Inflammation

The *in vitro* studies, as presented in **Table 1**, can offer the possibility to investigate and identify the diversity of related diseases in which GP exerts the optimum antioxidant and anti-inflammatory effects.

Table 1. *In vitro* beneficial actions of grape pomace in oxidative stress and inflammation.

Grape Pomace Variety	Models	Polyphenols Content	Antioxidant and Anti-Inflammatory Effects	References
		Red Grape Pomace Variety		
Batiki Tyrnavou variety (Greece)	**Tert-butyl hydroperoxide induced-oxidative stress in C2C12 muscle cells and EA.hy926 endothelial cells**	**Flavanols, (catechin and epicatechin), anthocyanidins, anthocyanins, flavonols (quercetin) phenolic acids (gallic acid and caftaric acid)**	**-decreased ROS levels in muscle cells -decreased TBARS and carbonyls levels in both cells line -increased GSH levels in both cells line;**	**[1]**
Tinta Cao and Cabernet Franc (USA)	**CA77 cell line**	**-**	**-decreased CGRP levels**	**[2]**

Grape Pomace Variety	Models	Polyphenols Content	Antioxidant and Anti-Inflammatory Effects	References
Tempranillo variety (University of Burgos, Spain) -WGPI-gastrointestinal digestion; WPF—colonic fermentation	**Hyperglycemic treatment in EA.hy926 endothelial cells**	**Phenolic acids, flavanols, stillbenes, flavonols**	**-increased mRNA Nrf2 levels, pNrf2/Nrf2 ratio; -increased pAkt/Akt ratio; -decreased pIκBα/IκBα and pIKK/IKK ratio, mRNA COX2, NOX4, SOD2 levels; -increased mRNA SIRT1, HO-1, CAT, NQO1 levels, GSH/GSSG ratio; -increased mRNA GS, GR levels in WGPI; -increased phospho-p38-MAPK/p38-MAPK ratio in WPF; -decreased mRNA NF-κB levels and pNF-κB p65/NF-κB p65 ratio in WPF; -increased mRNA GCLC, GS, GR, SOD, GPx1 levels in WPF;**	**[3]**
Carignan variety (Northern Tunisia)	**-6-hydroxydopamine-induced oxidative stress in mesencephalic cells (dopaminergic cells) -6-hydroxydopamine-induced oxidative stress in dopaminergic cells derived from stem cells**	**-**	**-increased cell viability in mesencephalic primary cells; -decreased ROS production in stem cells; -decreased phospho-NF-κB p65 translocation**	**[4]**
	White grape pomace variety			
Batiki Tyrnavou variety (Central Greece)	**Bovine spermatozoa incubated with different GP concentrations**	**-**	**-decreased MDA levels;**	**[5]**
	Red and White pomace variety			
White grape pomace (Moscato branco) and mixed grape pomace (red + white) Enzymatic hydrolysis treated fractions	**IL-1β treated Caco-2 cells**	**Quercetin, catechin, resveratrol, gallic and caffeic acids, trans-resveratrol, rutin and procyanidin B2**	**-decreased ROS in all fractions (100-200 µg/mL); -decreased NF-κB, PGE2 levels in all fractions; -significantly greater decrease of IL-8 levels in mixed grape pomace with or without enzymatic hydrolysis;**	**[6]**

Abbreviations: CAT—catalase; CGRP—calcitonin gene-related peptide; COX 2—cyclooxygenase 2; GR—glutathione reductase; GS—glutathione syntase; GCLC—glutamate-cysteine ligase catalytic subunit; GPx1—glutathione peroxidase 1; GSH—glutathione; GSSG—glutathione disulfide; HO-1—heme oxygenase 1; MDA—malondialdehyde; NF-κB—nuclear factor kappa-light-chain-enhancer of activated B cells; NF-κB p65—nuclear factor kappa-light-chain-enhancer of activated B cells transcription factor; NOX4—nicotinamide adenine dinucleotide phosphate oxidase 4; NQO1 —nicotinamide adenine dinucleotide plus hydrogen quinone oxidoreductase 1 mRNA Nrf2—messenger ribonucleic acid nuclear factor erythroid 2-related factor 2; p38-MAPK—p38mitogen-activated protein kinase PGE2—prostaglandin E2; pAkt—phosphorylated protein kinase B; pIκBα—phosphorylated inhibitor of kappa B; pIKK—phosphorylated IκB kinase; pNrf2—phosphorylated Nrf2 ROS—reactive oxygen species; SIRT1—sirtuin 1; SOD2—superoxide dismutase 2; TBARS—thiobarbituric acid reactive substances; TNF-α—tumor necrosis factor alpha.

The *in vitro* beneficial action of GP was studied by Goutzourelas et al. (2015) [1]. They investigated an extract of red GP on muscle and endothelial cells using non-cytotoxic doses to check the effect of GP polyphenols extract on cells' antioxidant enzymes [1]. The red GP extract was investigated as a mixture of compounds that contained phenolic acids (caftaric acid, gallic acid), anthocyanins, flavanols (epicatechin and catechin), flavonols (quercetin), and anthocyanidins. It was observed that GP treatment increased Glutathione S-transferase (GST) and GSH levels in both cell lines. CAT levels

were decreased in endothelial cells, while in muscle cells it showed no significant differences. SOD and HO-1 presented no differences in any population. An explanation for these inconstant findings, in which some of the antioxidant enzymes are not modified, is the ability of GP to enhance other antioxidant systems (GSC, GSH) [1] (**Table 1**). Another *in vitro* study, of Pop et al. (2022), investigated the antioxidant effect of red GP (mixture of Pinot Noir, Cabernet Sauvignon, Feteasc㠠Neagră, and Mamaia cultivars) and white GP (mixture of Sauvignon Blanc and Muscat Ottonel cultivars) added to a mouthwash on both H_2O_2 exposed and non-exposed fibroblast cells [7]. They observed that both red grape pomace (RGP) and white grape pomace (WGP) decreased ROS levels in a dose-dependent matter (100 < 200 < 300 µg/mL). Similar to the non-exposed condition, in the presence of H_2O_2, red GP and white GP led to a significant decrease in ROS levels, the only difference being that while red GP effect was dose-dependent, and white GP produced a non-dependent action [7]. Moreover, they also studied the anti-inflammatory effects of these extracts on lipopolysaccharides (LPS) induced inflammation in cells [7]. It was observed that while in the case of white GP a dose of 100 µg/mL was sufficient to induce a significant reduction of interleukin (IL) -8 levels, for red GP was necessary a higher dose of 200 µg/mL. At the dose of 300 µg/mL, both extracts significantly reduced IL-8 levels, but not even the highest dose did significantly reduce the levels of IL-6. In the case of IL-1β, the lowest dose, 100 µg/mL, reduced its level to a similar one found in the non-exposed cells, while the doses of 200 and 300 µg/mL reduced, even more, the levels of IL-1β [7].

Marzulli et al. (2018), treated mononuclear cells with phorbol 12-myristate 13-acetate (PMA) to activate inflammation, and with different GPs (red Negroamaro cultivar or white Koshu cultivar) extracts (water, ethanol), to observe their immunomodulatory effects [8]. In terms of cytokine release, all GP fractions and extracts increased anti-inflammatory (IL-10) and pro-inflammatory (IL-12, IL-1β, IL-6, tumor necrosis factor-alpha (TNF-α)) cytokines. The water extracts of both GPs managed to increase T regulatory cells and forkhead box P3 (FoxP3) protein, which is responsible for the genes activity control that are involved in the immune system regulation. Another benefic effect of GPs extracts is FoxP3 increase which is a marker with a role in stabilizing the T regulatory cells' function. All extracts lowered the release of granzyme (GrB) compared to PMA treated group [8]. GrB is an enzyme secreted by cytolytic T cells with role in cell necrosis leading to harmful effects on homeostasis [8]. Regarding intracellular cytokines, the water extract of red Negroamaro GP increased TNF-α and IL-10 content in monocytes, while the red Negroamaro GP ethanol extract increased IL-12 and IL-10 levels in lymphocytes. Further, the white Koshu GP water extract increased monocyte levels of IL-10 and IL-12, while the white Koshu GP ethanol extract increased lymphocyte levels of TNF-α and IL-10. IL-10 was increased by both water or ethanolic, red or white GP extracts and as underlined by authors [8], the release of IL-10 by T cells and monocytes is a key step in maintaining the immune homeostasis. In conclusion, GPs extracts could induce immune homeostasis through the anti-inflammatory IL-10 secretion which counterbalances the pro-inflammatory cytokines (IL-12 and TNF-α) [8]. Another study that reinforces the anti-inflammatory effects of RGP from *Vitis vinifera* L. cv. Montepulciano d'Abruzzo on LPS-stimulated macrophages is that of Mollica et al. (2021). They observed that the extract significantly inhibited the release of cytokines (IL-6, TNF-α, and IL-1β), the maximal inhibitory action being at the dose of 100 µg/mL [9].

The possible potential impact of GP extracts on *in vitro* calcitonin gene-related peptide (CGRP) secretion was investigated as a potential mechanism to influence migraine [2]. The treatment of CA 77 cells with different red GP extracts showed a significant decrease in CGRP levels. CGRP is a gene that represents a key mediator of migraine-induced inflammation [2]. The results suggest that GP extracts had anti-inflammatory effect preventing the release of CGRP in migraine [8885].

White GP extract and a mixture of red and white GP extract, in different concentrations (100, 200, 500 µg/mL dry extract *w*/*v*), were added to Caco-2 cells after treatment with an inflammation inducer (IL-1β) to observe the effects on IL-8 secretion and NF-κB expression [10]. Grape pomaces were hydrolyzed enzymatically to determine if anti-inflammatory effects would be augmented. Both white and red GP contained quercetin, catechin, resveratrol, gallic and caffeic acids, trans-resveratrol, rutin, and procyanidin B2 [10]. All GP fractions (100, 200 µg/mL dry extract *w*/*v*) with or without enzymatic transformation decreased ROS levels, while treatment with GP extracts in higher concentration (500 µg/mL dry extract *w*/*v*) showed a considerable increase in ROS levels. Furthermore, NF-κB expression and prostaglandin E2 (PGE2) levels were significantly reduced in all fractions. At the same time, IL-8 secretion revealed a more substantial drop in enzymatically treated fractions of mixed GP, presenting beneficial effects of enzyme hydrolysis. The mixed GP had a more potent anti-inflammatory effect due to the high content of anthocyanins found in red GP [6].

Concerning the benefic antioxidant and anti-inflammatory GP actions, the literature presents a large variety of experimental settings that can be considered for future *in vivo* research. Also, it can be observed that there is still space for other hypotheses, for both red and white GPs, but especially for the white ones which were much less investigated.

2. In Vivo Beneficial Actions of Grape Pomace in Oxidative Stress and Inflammation

The effect of GP extracts on the pathophysiology of oxidative stress and inflammation in various types of diseases can be well documented using different *in vivo* experimental models. These types of studies are very important in deciding whether the GP can be further used in safe conditions in human clinical trials.

The antioxidant and anti-inflammatory effects of both fresh and fermented GP extracts (*Vitis vinifera* L. cultivars, Fetească neagră, and Pinot noir, from Romania) were investigated using and a rat model of induced inflammation by turpentine oil [11]. The administration of turpentine oil increased the total oxidative status, oxidative stress index and reduced total antioxidant reactivity [11]. Treatment with GP decreased total oxidative status and oxidative stress index in a dose-dependent manner, but total antioxidant reactivity was not modified. All GP's fractions significantly reduced malondialdehyde (MDA) levels. Total thiols were considerably lessened by turpentine, but GP managed to increase them in a concentration-dependent way. The same results were observed in the case of NOx production. 3NT was also increased by turpentine, but GP varieties decreased the levels. Due to higher phenolic content, the fresh extract showed a higher antioxidant effect. MDA is a lipid peroxidation waste product with hazardous potential for normal homeostasis. Thiols, under oxidative stress, manage to form disulphide bonds between them to reduce oxidative stress. NO presents a dual effect based on its concentrations. Small doses possess an antioxidant effect, while high doses can cause an increase in oxidative stress through the synthesis of new and stronger radicals. 3NT is a waste product resulting from tyrosine nitration induced by reactive nitrogen species [11]. The authors concluded that GP extracts could be used considered a potential agent in nutraceuticals formulation.

An interesting study that evaluates the effects of red GP flour dietary inclusion on growth, anti-inflammatory, antioxidant, innate-adaptive immunity, and on immune genes expression was performed on *Labeo rohita* fish against *Flavobacterium columnaris* induced infection [12]. Treatment with 200 and 300 mg GP flour showed a significant increase in GSH, SOD, and GPx activities as compared to regular diet or 100 mg GP supplementation, in both infected and uninfected groups. Regarding GP action on innate-adaptive immune activity, higher doses of GP (200, 300 mg) increased phagocytosis, alternative-complement pathway activity, raised IgM levels, and serum lysozyme (Lyz) activity when compared to regular diet or 100 mg GP supplementation in infected or uninfected group. In terms of immune-related genes, Lyz, (β-2 microglobulin) β-2M, 3rd component complement (CC3), and immunoglobulin M (IgM) gene expression pointed out a significant growth in infected fish with 200, 300 mg GP supplementation compared to other groups. However, the uninfected group treated with the same doses of GP showed higher gene expression than the infected group. Antioxidant related-genes were measured, and SOD, GPx, nuclear factor erythroid 2-related factor 2 (Nrf2), and (natural killer-cell enhancing factor β) NKEF-β were remarkably higher in all groups treated with raised doses of GP compared to 100 mg GP diet or regular diet in infected or uninfected groups. Furthermore, uninfected groups treated with high doses of GP showed a more significant increase in SOD and GPx expression levels. As for pro-inflammatory-related genes, IL-1β and TNF-α were not modified in any group. Hepcidin and toll-like receptor-22 (TLR22) expression were increased in infected and uninfected groups treated with a high dose of GP [12].

Therefore, in Rajković et al. (2022), GP was given to piglets to assess their positive effects on the animal organism without antibiotics side effects [13]. During the experiment tissue samplings (liver, jejunum, ileum) were collected on days 27/28 and 55/56, while blood samples were taken on days 6, days 27/28, and 55/56. Regarding antioxidant enzymes, GPx (GPx1-liver, GPx-2 jejunum, and ileum) wasn't different between diets, but the enzyme activity was significantly increased on days 55/56 compared to 27/28 [13]. About, SOD and Manganese Superoxide Dismutase (Mn-SOD) enzymes, there weren't any differences between diets in jejunum, ileum, and liver, but there was an increase between sampling dates, in days 55/56 compared to 27/28 in the liver. The copper superoxide dismutase system (Cu-SOD or SOD1) presented no distinction between any sampling days in the liver or ileum. CAT activity wasn't affected by any of the diets in the jejunum and liver, but there were differences between sampling days in the liver and ileum. TBARS concentrations weren't affected by diets in any organs, only in the jejunum between sampling days (decreased levels on days 55/56 compared to 27/28). GPx2 and SOD1 gene expression were modified at the jejunum level (decreased in days 55/56 compared to 27/28), while CAT expression presented the same results at the ileum level. In the liver, the authors have observed differences between samples for SOD1, CAT, and GPx1 in the liver, with a higher expression on days 27/28 compared to 55/56. In terms of inflammation, pig major acute phase-protein serum levels presented a decrease on days 55/56 and 27/28 compared to day 6 [13]. MDA serum levels decreased through sampling days while for SOD different fluctuations were noticed, without showing any significant values on day 55/56 versus other time points. As a speculative explanation for the variation of antioxidant enzymes decreasing it can be stated that the systemic presence of antioxidant substances can lead to a decreasing need for endogenous antioxidant enzymes production [13].

Another important direction in GP research is to check whether it is suitable to be used as an adjuvant treatment in different pathologies to reduce conventional drugs side effects. Thus, in Mossa et al. (2015) study, cypermethrin was given to female rats to observe toxic effects on the liver and kidneys, and white GP was added to check whether it can counter these toxic effects [14]. The assessment of kidneys and liver biomarkers showed a dose-dependent fall in liver enzymes: aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP), and a decrease kidneys urea nitrogen and creatine. Also, total proteins and albumin revealed a significant increase in GP treated group. The histological analysis pointed out significant changes due to inflammatory infiltrate in cypermethrin groups, while the GP supplemented group had regressed values for all biomarkers. Similar results were also observed in histological studies of kidneys samples. This may be due to the antioxidant effects of the white GP [14]. This study offers important evidence regarding the use of GP extract with hepatorenal protective activity and encourages future studies to investigate whether it can be used to reduce other drugs adverse reactions.

So far, the existing studies on GP suggest that through its anti-inflammatory and antioxidant effects, GP can be considered a potent agent that can contribute to the restoration of homeostasis to control levels or that can reduce different drug side effects (**Table 2**).

Table 2. *In vivo* beneficial actions of grape pomace in oxidative stress and inflammation.

Grape Pomace	Models	Polyphenols Content	Antioxidant and Anti-Inflammatory Effects	References
		Red grape pomace variety		
Tempranillo variety (Burgos, Spain)	**Spontaneously hypertensive rats**	**Proanthocyanidin, anthocyanins, quercetin**	**-TAC increased; -decreased lipid peroxidation and carbonyl groups; -increased NO levels -increased HO-1, SOD2, eNOS gene expression;**	**[15]**
Alicante and Pinot varieties (France) polyphenol-enriched Alicante	**Dextran Sulfate Sodium-Induced colitis in Wistar male**	**Anthocyanins**	**-improved histological score; -decreased MPO activity; -increased SOD activity in polyphenol-enriched Alicante; -decreased IL-1α, IL-6 IFN-γ levels; -decreased IL-1β levels in Alicante and Pinot; -decreased IL6, ICAM-1, MMP-9 gene expression; -decreased IL-1β, iNOS gene expression in Alicante and Pinot; -decreased TNFα, NFκB p65, COX2 gene expression in polyphenol-enriched Alicante;**	**[16]**
Malbec variety (Gualtallary, Mendoza, Argentina)	**High fructose diet-induced Metabolic syndrome in Wistar rats**	**Quercetin, epicatechin, catechin, trans-resveratrol, ferulic, gallic, caffeic, syringic, p-coumaric acids**	**-reduced CRP levels; -reduced NADPH oxidase activity; -increased adiponectin; -reduced resistin; -increased insulin sensitivity;**	**[17]**
Dimrit grapes variety	**96 laying Hens given different GP concentrations**	**Catechin, Epicatechin, Gallocatechin, Epigallocatechin, Phenolic acids, Gallic acid, Caffeic acid, p-cumaric acid**	**-decreased plasma MDA levels; -decreased egg yolk MDA levels;**	**[18]**
Red wine grape pomace	**18 crossbreed lambs given different GP diets (5%, 10%)**	**-**	**-increased TAOC and SOD, GPX activity in longissimus dorsi muscle; -decreased ROS and MDA levels in longissimus dorsi muscle;**	**[19]**

Grape Pomace	Models	Polyphenols Content	Antioxidant and Anti-Inflammatory Effects	References
Red wine grape pomace	24 crossbreed ram lambs under pen conditions given GP diets (5%, 10%)	-	-decreased MDA and ROS levels in lamb testes; -increased CAT, SOD, GPx4 activity in lamb testes; -increased TAOC (GP 10%); -increased SOD, GPx4 mRNA expression (GP 10%); -increased CAT, SOD, GPx4 protein abundance;	[20]
Tempranillo variety	Wistar rats given high-fat diet	-	-decreased IL-1β and TNF-α levels; -increased FRAP plasma and liver levels; -increased liver GSH/GSSG ratio; -decreased plasma and liver MDA and carbonyl groups levels; -decreased 8-hydroxydeoxyguanosine plasma levels;	[21]
Muscat Bailey A variety (Gyeongsangbuk-do, Korea)	High-fat diet induced obesity in male C57BL/6J mice	Catechins, resveratrol, flavonoids,	-decreased TNF-α, PAI-1 levels; -decreased liver NF-κB, IL-6 and TNF-α levels;	[22]
Cabernet Franc (Chrysalis Vineyards, Virginia)	C57BL/6NCr mice given high-fat diet	-	-decreased TNF-α, IFN-ɣ, IL-12β, PAI-1 and resistin levels	[23]
Red wine pomace	78 crossbreed piglet given apple or grape pomace	Flavanols	-decreased NF-κB mRNA expression in the stomach; -increased NF-κB and TNF-α mRNA expression in the liver and muscle; -decreased TNF-α and IL-10 mRNA expression in ileum; -increased IL-10 mRNA expression in the jejunum, colon, and liver;	[24]
Red dried grape pomace (*Vitis vinifera* L. variety)	20 Fresian cows given GP diet	Flavonoids, gallic acid, epicatechin	-lower MDA levels in the cheese from cow's milk that received GP; -lower thrombogenic index in cow's milk that received GP;	[25]
Pinotage variety (Bellevue Wine Estate, Stellenbosch, South Africa)	40 lambs given GP diets at different c% (0, 5, 10, 15, 20)	Proanthocyanidins, tannins	-increased antioxidant activity (15, 20% diets) within first 3 days of meat storage; -decreased TBARS levels of all diets from day 5 to day 9 of meat storage; -decreased carbonyl content in stored meat (10, 20%);	[26]
Pinotage variety (Bellevue, Beyers Kloof, Western Cape Province, South Africa)	Angus steer given dried grape pomace or dried citrus pulp	Proanthocyanidins, tannins	-decreased TBARS and carbonyl levels; -increased antioxidant activity;	[27]
Cencibel variety (Grupo Matarromera San Bernardo-Valbuena de Duero, Valladolid, Spain) Enzymatic hydrolysis treated fractions—tannase and carbohydrase enzyme complex—separately or combined	300 Cobb chicks given different GP c% (5, 10) diets—hydrolyzed/un-hydrolyzed	Gallic acid, Catechin, Epicatechin, Procyanidin B1, Procyanidin B2 Epicatechin-O-gallate;	-decreased MDA levels;	[28]

Grape Pomace	Models	Polyphenols Content	Antioxidant and Anti-Inflammatory Effects	References
Moschato variety Tyrnavos (Larissa prefecture, Greece)	30 female broilers given GP diet for 15 or 35 days;	-	-15 days GP diet: decreased TBARS plasma levels, increased GSH levels in kidney and spleen, decreased TBARS levels in pancreas and intestine, decreased CARB levels in the kidney; -35 days GP diet: increased GSH erythrocytes levels, decreased TBARS plasma levels, increased GSH levels in kidney, spleen, heart, lung, and liver, increased TAC levels in liver, spleen, and kidney, decreased H_2O_2 decomposition in the intestine, decreased TBARS levels in spleen, quadriceps muscle, and heart, decreased CARB levels in spleen and kidney;	[29]
Cencibel variety	180 broiler chicks given different GP diets doses (15, 30, 60 mg/kg) or Vitamin E;	Condensed tannins	-decreased MDA levels in refrigerated breast meat;	[30]
Cencibel variety (Vinícola de Castilla S.A.,Manzanares, Ciudad Real, Spain)	120 broiler chicks given different GP diets doses (5, 15, 30 mg/kg) or Vitamin E;	-	-decreased MDA levels in refrigerated breast and thigh meat (day 7); -decreased MDA levels in refrigerated breast meat (day 4);	[31]
Moschato variety (Tyrnavos Larissa, Greece)	24 piglets given GP diet (blood and tissue samples taken at 15 and 30 days post-diet)	-	-15 days GP diet: decreased TAC plasma activity, decreased CARB levels in spleen, brain and liver, decreased TBARS levels in brain, kidneys, stomach, heart, lungs, quadriceps muscle, and spleen, increased TAC levels in stomach and pancreas, decreased TAC levels in the brain, increased GSH levels, heart, liver, spleen, stomach, pancreas, lungs, brain and quadriceps muscle; increased H_2O_2 decomposition activity in kidneys and decreased in lungs and stomach; -30 days GP diet: decreased CAT erythrocytes activity, decreased CARB levels in spleen, brain, liver, lungs, quadriceps muscle, stomach, and pancreas, decreased TBARS levels in brain, liver, heart, lungs, quadriceps muscle, spleen, and pancreas; increased TAC levels in the quadriceps muscle, kidneys, lungs, stomach, and pancreas, decreased TAC levelsthe in brain, increased GSH levels heart, liver, pancreas, lungs, brain and quadriceps muscle, kidneys; decreased TAC levels in stomach and spleen; increased H_2O_2 decomposition activity in kidneys, quadriceps muscle, pancreas and decreased in lungs and brain;	[32]
Cencibel variety (La Mancha, España)	70 broiler chicks given GP diets doses (0, 30, 60 mg/kg)	Condensed tannins, hydrolysable tannins;	-reduced TBARS levels in raw chicken patties (storage day 13, 20); - reduced TBARS levels in cooked chicken patties (storage day 3, 6, 13, 20); -reduced TBARS levels in raw chicken patties (60 mg/kg—6 months storage); -reduced TBARS levels in cooked chicken patties (30, 60 mg/kg—6 months storage);	[33]

Grape Pomace	Models	Polyphenols Content	Antioxidant and Anti-Inflammatory Effects	References
Moschato variety (Tyrnavos Larissa, Greece)	**28 lambs given GP diet (blood and tissue samples taken at 27 and 55 days post-diet)**	**-**	**-27 days GP diet: increased CAT erythrocytes activity; decreased protein carbonyls level in the liver; increased TBARS activity in the brain; -55 days GP diet: reduced TBARS activity in liver, spleen, and heart; increased TBARS activity in the brain; decreased TAC in brain and liver; GSH levels increased in quadriceps muscle and spleen; decreased GSH levels in the liver;**	**[34]**
Carignan variety (Northern Tunisia	**Adult mice given 6-hydroxydopamine stereotaxic injection in midbrain (Parkinson disease model)**	**-**	**-increased SOD1 brain levels; -decreased neurons depletion in substantia nigra; -ameliorated motor impairment;**	**[9]**
		White grape pomace variety		
Koshu variety (Japan and Italy) Fermented or un-fermented fractions	**Female rats induced-allergic reactions (asthma and passive cutaneous anaphylaxis)**	**-**	**-decreased serum IgE levels; -decreased eosinophils levels in bronchial lavage; -decreased cutaneous reaction in time and dose-dependent manners; -decreased cutaneous reaction compared to Tannat or Negroamaro GP (red varieties)**	**[35]**

Abbreviations: AOPP—advanced oxidation protein product; CARB—protein carbonyls; CAT—catalase; COX 2—cyclooxygenase 2; CRP—C-reactive protein; DPPH—2,2-diphenyl-1-picrylhydrazyl; FRAP—ferric ion antioxidant reducing power; GP—grape pomace; GPx—glutathione peroxidase; ɣ-GCS—ɣ-synthase glutamyl cysteine; GSH—glutathione; GSSG—glutathione disulfide; GST—glutathione-s-transferase; HO-1—heme oxygenase 1; ICAM-1—Intercellular Adhesion Molecule 1; IFN-ɣ—interferon gamma; MDA—malondialdehyde; MMP-9—matrix metalloproteinase 9; MPO—myeloperoxidase activity; NADPH—nicotinamide adenine dinucleotide phosphate; NF-κB p65—nuclear factor kappa-light-chain-enhancer of activated B cells transcription factor; eNOS- endothelial nitric oxide synthase; iNOS—inducible nitric oxide synthase; NO—nitric oxide; oxLDL- Oxidized low-density lipoprotein; PAI-1—Plasminogen activator inhibitor-1; ROS—reactive oxygen species; SOD—superoxide dismutase; TAC—total antioxidant capacity; TAOC—total antioxidant capacity; TAS—total antioxidant status; TBARS—thiobarbituric acid reactive substances; TNF-α—tumor necrosis factor alpha.

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